STUDY REPORT SYNOPSIS

EBISU study

Change in symptom and quality of life in COPD by Budesonide/Glycopyrronium/Formoterol fumarate pressurized metered dose inhaler (BGF pMDI): a prospective, multi-centers, observational study

Milestones: Protocol Completion: 27 Oct 2021
First Patients In: 16 May 2022
Patients Enrolled 100%: 27 Feb 2023
Last Patients Last Visit: 30 May 2023
Data Base Lock: 25 Aug 2023
Statistical Analysis Data Available: 31 Oct 2023
Final CSR Report:16 Apr 2024

Phase of development: N/A

Sponsor: AstraZeneca

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This study was performed in accordance with ethical principles that were consistent with the Declaration of Helsinki and applicable legislation on Non-Interventional Studies. The Investigator performed this study in accordance with ethical guidelines for medical and health research involving human subjects. The final protocol of this study including the final version of the informed consent form (ICF) was approved or given a favorable opinion in writing by the ethics committee (EC) / institutional review board (IRB)/ independent ethics committee (IEC). The EC/IRB/IEC approved any amendment to the protocol and all advertising used to recruit patients for the study, according to local regulations.

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca (AZ) and opportunity to object.

Background/rationale:
The treatment goals for chronic obstructive pulmonary disease (COPD) are defined as two parts in Japanese guidelines: 1. Improvement of current status (i.e., improvement of patient-reported outcomes (PROs) such as health-related quality of life (HRQoL) and symptom, improvement and maintenance of physical activities) and 2. Reduction of future risk (i.e., prevention of exacerbation, suppression of disease progression and

extension of healthy life expectancy). Internal research indicated that the physicians in Japan, regardless of pulmonary specialists or non-specialists, put more emphasis on improvement of PROs than reduction of exacerbation or mortality, as reasons to choose new medication. This indicates the improvement of current status, such as PROs by pharmacological treatments could have an impact on the treatment choices of physicians, and the study on the improvement of PROs by BGF pMDI in the real world setting is necessary. EBISU was a prospective, multi-centers, observational study over 12 weeks in COPD patients who started BGFpMDI regimen in the real-world settings in Japan. This study was primarily aimed to investigate whether PROs had improved after the initiation of BGF pMDI in real world clinical settings. While the study was 12 weeks in duration, the initial 4 weeks were used to assess immediate onset of benefits while the full study length served to demonstrate durability in response.

Objectives:
Primary Objective:
To assess the change in the health status as measured by the COPD assessment test (CAT) over 12 weeks from the initiation of BGF pMDI in COPD patients.
Secondary Objectives:
1. To assess the change in the HRQoL as measured by St George's Respiratory Questionnaire (SGRQ) over 12 weeks from the initiation of BGF pMDI in COPD patients
2. To assess the change in the HRQoL as measured by the SGRQ at 4 and 12 weeks from the initiation of BGF pMDI in COPD patients
3. To assess the change in the health status measured by CAT at 4 and 12 weeks from the initiation of BGF pMDI in COPD patients
4. To assess the achievement of the minimal clinical important difference (MCID) of the SGRQ at 4 and 12 weeks from the initiation of BGF pMDI in COPD patients
5. To assess the achievement of MCID of the CAT at 4 and 12 weeks from the initiation of BGF pMDI in COPD patients

Our hypothesis was that the initiation of BGF pMDI would be associated with an improvement of PROs in patients.

Study design:
This is a 12-week, multi-center, prospective observational study in which a total number of 107 patients were planned to enroll. Adult outpatients with COPD without asthma history and who initiate on BGF pMDI as decided by the physicians in their routine clinical care were consecutively invited for this study. Investigators (physicians) made screening their patients prior to the study entry and made informed consent explanation at their usual visit timing to all the eligible patients. After fulfilling eligibility criteria at study entry, the patients were enrolled in the study and the investigators followed up the patients as in routine clinical practice and collected the data at baseline, at week 4 and week 12.

Data source:
The study sites were selected where BGF pMDI was used as a treatment option for COPD patients and lung function (i.e., spirometry) for COPD patients was examined in daily clinical practice.

Study population:
The investigators in this study enrolled adult patients without asthma history with COPD who initiated BGF pMDI in the clinics/hospitals.

Inclusion criteria:
Patients enrolled in this study satisfied all of the following:
1. Male or female patients aged ≥40 years old at study entry
2. Patients diagnosed with COPD (based on post-bronchodilator forced expiratory volume 1_1/flow volume curve percent predicted forced (FEV_1/FVC) <70% in the past 5 years and current or former smokers with a smoking history of ≥10 pack-years in the past)
3. Patients who were on the new prescription of BGF pMDI 320/18/9.6µg twice daily as per the physician's decision, at baseline
4. Patients with CAT≥10 at study entry
5. Patients who were capable to fill patient-reported outcome measures (PROMs) physically and/or mentally as judged by investigators
6. Patients who provided written informed consent prior to the study entry

Exclusion criteria:
Patients who met any of the followings were excluded from this study:
1. Patients diagnosed as asthma by investigator's judgement at and/or before study entry
2. Patients who participated in any interventional clinical studies and/or any relevant studies (quality of life (QoL) and respiratory research) during the 12 weeks before the study entry and/or during this study
3. Patients who used inhaled corticosteroid (ICS)+long-acting β_2-agonist (LABA)+long-acting muscarinic antagonist (LAMA) therapy including open triple and closed triple before the study entry
4. Patients with history of COPD exacerbation during 4 weeks before the study entry
5. Patients with very severe comorbidities or status which would impact on QoL evaluation judged by investigators (e.g., heart failure, malignancy, receiving home oxygen therapy, pneumonia)

Statistical methods:
All data including patient characteristics at baseline were summarized using appropriate descriptive statistics. Full analysis set (FAS) included all the enrolled patients who met eligibility criteria, received the treatment, and of whose any outcome data were obtained. All tests were made as 2-sided significance level 5%. An additional analysis was performed.
Primary Objective:
CAT scores were analyzed using linear model for repeated measures including baseline as a covariate. Mean of available CAT scores over week 4 to 12 were used as the post-baseline in this analysis. Based on the linear model, the adjusted mean change from baseline over 12 weeks was estimated. To compare the difference between baseline and post-baseline, 2-sided t test p-value, and 95% t-type confidence interval (CI) for least squares means of the difference were calculated.
Secondary Objectives:
SGRQ total scores were analyzed similarly to the analysis for CAT scores described in primary objective. SGRQ and CAT scores were analyzed using mixed model for repeated measures (MMRM) including baseline as a covariate. For week 4 and 12 timepoints, available data closest to the target timepoint were used in this analysis. The model analysis with variance-covariance structure was made. The unstructures firstly assumed. If not converged, the first order autoregression assumption was applied. Finally, compound-symmetry assumption was applied if not converged. Kenward and Roger's method was used to adjust the estimator of the covariance matrix of the fixed effect and the degrees of freedom for t test in the MMRM model. Based on the MMRM, the adjusted mean changes from baseline at week 4 and 12 were estimated. Two-sided t test p-value and the 95% t-type CI for least squares means of the changes were calculated. The number and proportion of patients who achieved changes from baseline greater than or equal to MCID in SGRQ and CAT scores (i.e., changes from baseline in SGRQ scores ≥4 and changes from baseline in CAT scores ≥2) at each timepoint were summarized. The Clopper-Pearson exact 95% CI for the single proportion was also presented.

Results:
Patient characteristics and adherence of inhaler treatment:
In this study, 106 patients were enrolled, and 102 patients were included in the FAS after excluding 4 patients who never visited the institution after enrollment. The mean age of the patients at baseline for the FAS was 73.8 years, 89.2% were male, the mean body-mass index (BMI) was 22.45 kg/m^2 (98 patients), and the percentage of current smokers was 31.4%. Patients with emphysema as COPD phenotype accounted for 83.3%, with a mean expiratory volume % in one second (%FEV_1) of 57.66% (67 patients). COPD severity was Global Initiative for Chronic Obstructive Lung Disease (GOLD) I in 10.4%, GOLD II in 56.7%, GOLD

III in 22.4%, and GOLD IV in 10.4% (67 patients). The proportion of patients who had a history of exacerbation in the past 12 months was 6.9%, and the proportion of patients who were treated with LAMA+LABA before enrollment in the study was 69.6%. The mean of CAT scores at baseline was 15.6 and the mean of SGRQ scores at baseline was 33.307. The administration status of BGF pMDI in this study, as assessed by the test of the adherence to inhalers (TAI) score, was adherent in approximately 60% and non-adherent in approximately 15% at 4 and 12 weeks from the initiation of BGF pMDI.

CAT scores outcome:

The adjusted mean changes from baseline in the CAT scores over week 12 were -2.9 (95% CI, -3.9 to -1.9, p<0.001). The adjusted mean changes from baseline in the CAT scores at week 4 and 12 were -2.8 (95% CI, -3.8 to -1.8, p<0.001) and -2.9 (95% CI, -4.1 to -1.7, p<0.001), respectively. The achievement rates of MCID (change of ≥2 from baseline) in the CAT scores at week 4 and 12 were 61.4% (95% CI, 51.2 to 70.9) and 63.4% (95% CI, 52.8 to 73.2), respectively. The adjusted mean changes from baseline in the CAT scores over week 12 significantly decreased in all subgroups, except for the subgroups with chronic bronchitis, exacerbation history in the previous 12 months, and maintenance therapy with ICS+LABA.

SGRQ scores outcome:

The adjusted mean changes from baseline in the SGRQ scores over week 12 were -2.707 (95% CI, -4.534 to -0.880, p=0.004). The adjusted mean changes from baseline in the SGRQ scores at week 4 and 12 were -2.353 (95% CI, -4.261 to -0.446, p=0.016) and -2.940 (95% CI, -5.271 to -0.609, p=0.014), respectively. The achievement rates of MCID (change of ≥4 from baseline) in the SGRQ scores at week 4 and 12 were 33.7% (95% CI, 24.4 to 43.9) and 39.1% (95% CI, 29.1 to 49.9), respectively.

Conclusion:

Under clinical practice in Japan, statistically significant improvements were seen in symptoms and HRQoL at 12 weeks from the initiation of BGF pMDI in COPD patients with residual symptoms excluding pre-existing and current asthma.

Publications:

Not applicable.